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TITLE: Benefits, Harms, and Costs of Osteoporosis Screening in Male Veterans

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14. ABSTRACT

This is a longitudinal cohort study of approximately 5,000,000 screened and non-screened for osteoporosis, older veterans who received care within the VA system during the study period, followed for up to 10 years to measure fracture rates, mortality rates, treatment-related harms, and cost. In the past year, over 200 hundred variables were defined and data for each variable has been pulled with comparisons underway. Identification of the screened cohort is near completion. The propensity score model has been developed and analysis to estimate the impact of osteoporosis screening and treatment on fracture and mortality rates has begun. Additional analyses will determine whether bisphosphonate treatment is associated with a change in fracture rates or mortality. Treatment-related harms will be examined using time to event modeling with receipt of bisphosphonate as the time varying covariate of interest. The process of defining harms variables is underway with anticipated completion imminent. Costs will be measured prospectively for all subjects in the cohort, and adjusted for important covariates. A cost differential for screened and unscreened populations will be calculated. To estimate health system costs under varying screening thresholds and conditions we have employed modeling analyses. Cost variables are currently being defined.

15. SUBJECT TERMS

Osteoporosis, Males, Screening

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1. INTRODUCTION:

Osteoporotic fractures are a major and under-recognized problem in older men.[1] Osteoporosis is particularly prevalent in the VA system; more than half of male veterans over age 50 years have osteopenia or osteoporosis, and nearly 12% of those over age 75 years have osteoporosis, a rate nearly double the non-veteran population.[6] Despite the widespread recognition that osteoporosis is an important disease in men, there is no clear consensus on the appropriate approach for the primary prevention of osteoporotic fractures. While clinical practice guidelines in women uniformly endorse osteoporosis screening beginning at age 65 years,[11] clinical practice guidelines for men vary substantially in the recommended selection of the screening population, and indeed, on whether or not sufficient evidence exists to support osteoporosis screening at all. Current recommendations include screening all men at a given age [National Osteoporosis Foundation (NOF), Canadian Medical Association (CMA)], or selecting men based on the presence of osteoporosis risk factors [VA HSR&D, American College of Physicians (ACP)].[12-15] In the U.K., clinical risk factor scoring systems such as the Fracture Risk Assessment Tool (FRAX) are used to stratify patients; high risk groups receive treatment without further screening, intermediate risk groups go on to Dual Energy X-ray Absorptiometry (DXA) screening, and low risk groups receive no further screening.[15] Most recently, the United States Preventive Services Task Force (USPSTF) completed a systematic review of osteoporosis screening and treatment in men, and concluded that there was insufficient evidence to recommend for or against screening.[16] This conclusion was also adopted by the VA National Center for Health Promotion and Disease Prevention. This project will develop a large database combining Veterans Affairs and Centers for Medicare and Medicaid Services (CMS) data to quantify the benefits, costs, and harms of osteoporosis screening among men. We will use this database to determine the benefits of osteoporosis screening, including rates of fractures and mortality. We will quantify the harms of osteoporosis screening and treatment, including rare but important side effects such as heart disease, esophageal cancer, and atypical fractures. We will prospectively measure healthcare costs in the screened and unscreened individuals, and model the impact of different screening selection criteria on healthcare system costs. The goal is to develop evidence-based male osteoporosis screening recommendations that optimize benefits to patients, while minimizing harms and health system costs.

2. KEYWORDS:

Osteoporosis
Males
Veterans
Screening
Harms
Costs
Treatment
Fractures
Benefits
Propensity

3. OVERALL PROJECT SUMMARY:

The Current Objectives are unchanged from prior reports; we will quantify the benefits, harms, and costs of osteoporosis screening in a large cohort of older male Veterans. We will create the largest dataset currently available about osteoporosis in men, including medications, co-morbidities, fractures, and costs.

Summary of Results. The number of males eligible for the study was much larger than anticipated at 5,036,636, with more than 110,000 unique individuals with DXA results and 595,579 unique individuals with fractures.

While awaiting completion of NLP, pre-planned secondary analysis of fracture correlations was completed. Over the study period 595,579 (11.8%) men suffered 1 or more fractures and 140,905 (2.8%) suffered 2 or more fractures. Hip fracture was the most common specific fracture type (49% of individuals with fracture), followed by spine (31%), femur (26%) and shoulder (21%). The fracture types most highly correlated with hip fracture were pelvic/acetabular (Pearson coefficient 0.25, $p<0.0001$), femur (0.16, $p<0.0001$), and shoulder (0.11, $p<0.0001$). Odds ratios and kappa statistics (reflecting the proportion of potential agreement above chance) for each fracture type with hip fracture are reported below. Latent class analysis revealed good loading onto a single factor (rho estimates <0.10 or >0.90).

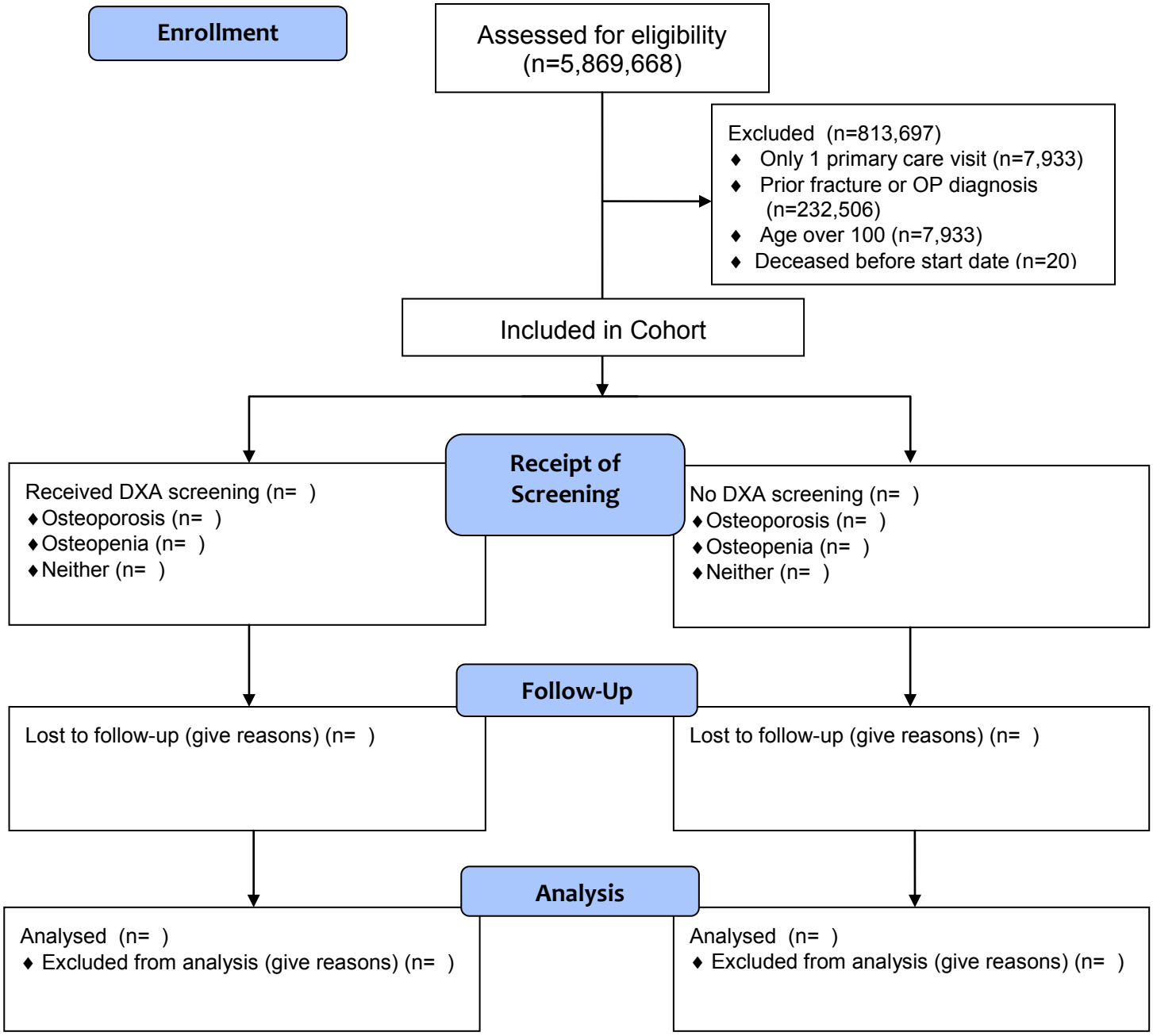
Progress and Accomplishments. The progress on each item of the approved scope of work is outlined in the table below. The final dataset is nearly complete, Natural Language Processing of the DXA results is completed with excellent validation measures, and coding for the propensity score is underway. Our first analysis has been presented at the annual meeting of the American Society of Bone and Mineral Research, and a publication is in preparation.

Methodology. Because of the larger than expected number of male Veterans with DXA screening, we will use a case control analysis strategy to decrease the number of men in the cohort and therefore avoid computing inefficiencies. Propensity score for DXA screening will be calculated for each calendar year for all cohort members, stratified by medical center, or if there are insufficient numbers of screened individuals in a calendar year, by VISN. Greedy matching will be employed to match each screened individual with up to 3 unscreened controls. Cox proportional hazards modeling will be used to calculate the hazard ratio for fracture in screened compared to unscreened individuals with the same propensity scores, and therefore with key confounders balanced between groups. Sensitivity analyses will exclude potentially traumatic fractures, include only those appropriately screened and treated, and incorporate FRAX scores into the model. Total health annual care costs and fracture related costs will be compared for cases and controls, incorporating known harms of treatment.

Problems and Delays.

- Space issues on servers has caused delays in the collection of cost variables
- NLP validation took a great deal longer than anticipated
- Some key variable data (lab results, costs) has been corrupted at the Austin site; we are working with them to restore this data.

CONSORT Flow Diagram



Task	Methods	Outcome/Deliverable/Product	Status
Milestone 1. Regulatory Approval, CMS and VA data requested and obtained. (months 1-6)			
Submit IRB and Human Subjects initial and continuing reviews at Durham VAMC and Salt Lake City VAMC (month 1-4)	Regulatory document completion, human subjects training	Maintenance of IRB approval at all sites engaged in research, study binder, personnel training up to date	Complete
Request Corporate Data Warehouse (CDW), and 1994-1999 Austin data (month 1-3)	Data Access Request Tracker (DART) system	Finder file of all Veterans in study period meeting eligibility criteria developed	Complete
Request Medicare (CMS) data from VA Information Resource Center (VIReC) (month 4-6)	Per VIReC Medicare data request process, using finder file developed from Austin data	Medicare data on eligible subjects downloaded to Durham VA server	Complete
Develop data management and security standard operating procedures (SOPs) (month 1-6)	Modification of existing and creating new SOPs as needed to describe data management practices	• Secure server files created and maintained • Clear procedures for data cleaning and management tasks documented	Complete
Milestone 2. Dual Energy X-ray Absorptiometry (*DXA*) data extracted and cleaned, VA and CMS data cleaned and ready for merge with DXA data (months 1-12)			
Extract DXA data from eligible subjects (month 1-6)	Natural language processing used to extract DXA results from text notes in radiology and consultation records	Dataset containing DXA results from all eligible subjects assembled.	Complete
Clean and validate DXA data (month 6-12)	Random subset of records hand pulled to calculate validations statistics	• Accuracy, Precision, Recall, and F measure calculated for DXA dataset. • DXA dataset is cleaned a ready for merge with VA and CMS files	Complete
VA database variables cleaned and validated (month 6-12)	Outlier variables are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Clean database of VA variables created and ready to merge with CMS and DXA files	Complete, except cost variables due to issues above.
CMS database variables cleaned and validated (month 6-12)	Outlier variables are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs	Clean database of CMS variables created and ready to merge with CMS and DXA files	Complete

	developed above. Missing variables are imputed if indicated.		
Milestone 3: Utilization and cost measures constructed for both VA and CMS data, and VA and CMS data files merged. (months 9- 18)			
Construct utilization and cost measures for VA database. (months 9-15)	Fracture related costs will be summarized across VA and non-VA contracted care using ICD9 and CPT codes and aggregated across inpatient and outpatient fields annually for each subject	Fracture-related costs to VA calculated for eligible subjects	In process
Construct utilization and cost measures for CMS database. (months 9-15)	Fracture-related costs to Medicare will be identified using ICD-9 codes and surgical procedure codes. Total costs to Medicare will be aggregated using the Beneficiary Annual Summary File, and aggregating the positive values from each of the following variables for the year.	Fracture related costs to CMA calculated for eligible subjects	In process
VA and CMS data files merged (month 15-18)	Using unique subject identifiers, CMS and VA data files will be merged, and cleaned using SOPs.	Cleaned database containing relevant VA and CMS variables created for all eligible subjects	Complete except cost variables
Milestone 4: Final analytic file completed. (month 21)			
DXA data merged with combined VA and CMS files (month 18-19)	Using unique subject identifiers, DXA data files will be merged with the main analytic file, and cleaned using SOPs.	Database containing all VA, CMS, and DXA result variables ready for cleaning	Complete
Merged file cleaned, data inconsistencies identified and cleaned using SOPs. (month 20-21)	Contradictory or multiple variables across files are identified using graphical and numerical methods, and confirmed, replaced or deleted per the SOPs developed above. Missing variables are imputed if indicated.	Cleaned database containing relevant VA and CMS variables and DXA results is ready for analysis	In process
Data de-identification of merged file completed according to SOPs (month 21)	Using current VA Information Security Officer guidance, merged datafile will be stripped of HIPAA key identifiers to create a limited data set	Cleaned dataset created with risk of subject identification and loss of privacy minimized	In process
Milestone 5: Analyses for specific aims completed. (month 30)			
Analyses for specific	A "propensity to be	• Hazard ratio reflecting risk	Propensity score

aims 1-2 (benefits and harms) completed. (months 21-30)	screened" model will be developed for each VAMC (strata) based on their osteoporosis and fracture risk factors. This screening propensity score will be used as a further stratification variable in Cox Proportional Hazards models, with receipt of DXA as a time-varying covariate, to estimate the impact of osteoporosis screening and treatment on fracture rates, mortality rates, and treatment-related harm outcomes.	of fracture and all-cause mortality (dependent variables) in screened and unscreened individuals, adjusting for important covariates including bisphosphonate treatment • Hazard ratio reflecting risk of harm in treated vs. untreated individuals, adjusting for important covariates (dependent variables include cardiovascular events, esophageal cancer, atypical fractures)	coding in process
Analyses for specific aim 3 (costs) completed. (months 21-30)	We will calculate VA and Medicare fracture related resource utilization costs as well as total VA and Medicare resource utilization costs for subjects in five year increments. Costs to the VA and costs to Medicare will be modeled separately and also aggregated to understand overall costs across the two public insurers.	• Cost to VA, Medicare, and total costs of different strategies of osteoporosis screening in male veterans	In process
Milestone 6: Result dissemination, final report completed. (month 36)			
Summary results (technical reports) of specific aims 1-3 written. (month 30-33)		Executive summary and technical report created for presentation to relevant stakeholders	
Technical reports presented to key stakeholder groups identified by advisory board members. (months 33-36)		• Report presented to VA National Center for Health Promotion and Disease Prevention • Report presentated to VA Pharmacy Benefits Management	
Scientific presentations and articles for peer review drafted on specific aims 1-3. (months 30-33)		• Results presented at American Society of Bone and Mineral Research, VA Health Services Research and Development, or other professional meetings	First paper presented at American Society of Bone and Mineral Research on Secondary analysis

4. KEY RESEARCH ACCOMPLISHMENTS:

- Variable coding and cleaning continues, about 95% completed with primarily cost variables remaining; unique fracture definition has been refined
- FRAX data has been tested with good results
- New consort numbers- from 5.5 million to 5.0 million with elimination of additional fractures and other exclusion criteria
- NLP coding complete

5. CONCLUSION:

The study is compiling the largest administrative database of men with osteoporosis to answer key questions about screening, treatment and costs. Despite delays related to the complexity and size of the database, we anticipate that analyses will be completed on schedule, and results presented in 2015.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

ASBMR Abstract: Correlation of Other Fracture Types with Hip Fracture: Toward a Rational Combined Hip Fracture Endpoint

7. INVENTIONS, PATENTS AND LICENSES:

Nothing to report.

8. REPORTABLE OUTCOMES:

Nothing to report.

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10. APPENDICES:
None